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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER	
ZARA, J	
ART UNIT	**PAPER NUMBER**
1635	4

DATE MAILED: 09/11/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

F 10

Office Action Summary

Application No.	Applicant(s)
09/522,278	O'Hare et al.
Examiner	**Group Art Unit**
Zara, Jane	1635

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 1-23 is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-23 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

☒ Notice to Comply

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Claims 1-23 are pending in the instant application.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Great Britain on March 10, 1999 and December 24, 1999. It is noted, however, that applicant has not filed a certified copy of these applications as required by 35 U.S.C. 119(b), therefore the claim for priority has not been perfected.

Specification

Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. (i.e. See claim 3.) See the accompanying Notice to Comply.

Claim Objections

Claim 8 is objected to because, in line 2, "oglionucleotide" must be replaced with --oligonucleotide--.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 18, 19, 22 and 23 are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01.

The omitted steps in claims 18, 19 and 22 are those which are involved in making aggregates, as well as those steps which ensure an exclusive particle size of 0.1 to 5 microns.

The omitted steps in claim 23 are those which promote disaggregation of the composition of the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to

the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-10 and 12-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over O'Hare *et al* in view of Schwartz *et al*.

The claims are drawn to compositions comprising aggregates of the transport functional domain of VP22 polypeptide and an oligonucleotide such as an antisense containing a phosphorothiate internucleoside linkage, or which oligonucleotide may alternatively encode a protein or peptide, and which aggregate is encapsulated in a liposome, and wherein the aggregate is delivered to target cells. The claims are also drawn to a method of making said aggregated compositions comprising mixing the components.

O'Hare *et al* teach methods of delivering compositions to target cells, which compositions comprise VP22 polypeptides with a functional binding domain, which may or may not be covalently attached to another peptide or protein, or may be attached or associated with a polynucleotide, which polynucleotide encodes a desired molecule, such as a protein or peptide (abstract; page 5, line 18-page 7, line 10; page 16, line 26-page 17, line 16; page 25, line 6-page 27, line 34).

O'Hare *et al* do not teach methods of making aggregates comprising liposomes, VP22 and polynucleotides, nor do they teach the labeling of the oligonucleotides, nor compositions comprising antisense molecules containing modified internucleoside linkages.

Schwartz *et al* teach methods of making and using aggregations comprising liposomes, proteins, peptides, glycoproteins and polynucleotides, which polynucleotides include antisense or ribozyme molecules which contain phosphorothioate internucleoside linkages, which oligonucleotides contain a detectable label, and which aggregates are used for cellular delivery of said compositions (column 9, line 57-column 15, line 67; column 19, example B).

It would have been obvious to one of ordinary skill in the art to make and use aggregated compositions comprising the binding domain of the VP22 polypeptide and further comprising a polynucleotide, and/or another peptide or protein, because such compositions had been taught previously by O'Hare *et al* for delivery to target cells. One of ordinary skill in the art would have been motivated to use such compositions for cellular delivery because such transduction domains as the binding domain of VP22 have been used for crossing target cell membranes, as taught previously by O'Hare *et al*, and therefore the inclusion of VP22 within such compositions was found to enhance the cellular uptake of the compositions, and furthermore also found to enhance localization of the complexes or aggregates within the nuclei of target cells. One of ordinary skill in the art would have expected that incorporation of oligonucleotides and other proteins into such compositions would enhance the cellular uptake of these oligonucleotides and desired effector proteins by the target cells, where the oligonucleotides may then act to inhibit gene expression if

they are antisense or ribozymes, or where the oligonucleotides are translated into functional proteins which they encode, which delivered or expressed proteins then exert their effects onto the target cells upon cellular delivery and uptake. One of ordinary skill in the art would have been motivated to include liposomes within these cell delivery compositions because it was known in the art that liposomes aid in cellular delivery of target oligonucleotides and proteins by fusing with the target cell membranes. One of ordinary skill in the art would have expected that aggregates form upon mixing of the amphipathic (cationic) liposomes with the (anionic) polynucleotides and proteins or polypeptides because such aggregation is well known in the art and has been taught previously by Schwartz *et al* and the references contained therein. One of ordinary skill in the art would have been motivated to include a detectable label within the polynucleotide in order to visualize the amount and subcellular localization upon cellular uptake of the composition, since such visualization or detection was a routine matter in the art and had been shown previously by Schwartz *et al.*

Therefore, the invention would have prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over O'Hare *et al* and Schwartz *et al* as applied to claims 1-10 (and 12-24) and further in view of Moyer *et al.*

O'Hare *et al* and Schwartz *et al* are relied upon as set forth in the 103 rejection above.

These references do not teach the incorporation of a cleavage susceptible amino acid sequence adjacent to the VP22 transport polypeptide within the aggregated compositions.

Moyer *et al* teach the incorporation of cleavable linkages within various constructs which are destined for target cell, whereby cleavage occurs within the target cells by the appropriate enzymes, and the joined polypeptides or proteins are released (column 16, lines 40-49).

It would have been obvious to one of ordinary skill in the art to make and use aggregated compositions comprising liposomes, the binding domain of the VP22 polypeptide and further comprising a polynucleotide and another peptide or protein, because such compositions had been taught previously by O'Hare *et al* for delivery to target cells. One of ordinary skill in the art would have been further motivated to make and use such aggregates further comprising a cleavable linkage between the VP22 polypeptide and the other protein, because such cleavable linkers have been taught previously by Moyer *et al*. One of ordinary skill in the art would have expected that such linkages would be cleaved within the target cell by appropriate enzymes, for instance, and the linked protein would then be liberated or released from the aggregate because the tether which held it to the aggregated VP22-polynucleotide-liposome complex has been removed, allowing for the diffusion of the liberated protein from the aggregated complex, whereby the protein can then exert its effect within the cell, free from the complex, as had been taught by Moyer *et al*.

Therefore, the invention would have prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(703) 306-5820.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott, can be reached on (703) 308-4003. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

JZ

September 7, 2000

REMY YUCEL, PH.D
PRIMARY EXAMINER